Chapter 1

General Introduction

Homeostasis of human body face many challenges in adverse internal physiological and extreme environmental conditions. The thermal stability and the drug transport mechanism of the biological tissues under these unfavourable conditions are considered to be important areas of research and development. Such challenges are exacerbated when two stressors are experienced simultaneously and each stimulus evokes opposing physiological responses. Thermal disturbances are more pronounced in the eye and peripheral regions of human body due to an insufficient blood flow and the exposure of these organs to the surrounding conditions. In biological systems, which are not amenable to direct investigation, such as human eye and human skin, computational modelling is the preferred tool to represent the heat and drug transport phenomena. Thermal modelling of the dermal regions and eye are important as it can provide one with a tool to investigate the effect of external heat sources as well as in predicting the abnormalities within these systems. The drug intake and its absorption, excretion and concentration at different compartments of the organism need a serious attention for the normal functioning of the body. Thus, it is imperative to establish mathematical framework of these situations using latest and effective mathematical tools.

In order to address various issues related to the heat and drug diffusion in human body, a number of mathematical models
were formulated and illustrated in the thesis which include:

(i) Drug diffusion through blood stream and tissue medium using compartment modelling.

(ii) Mathematical models on drug diffusion in human body through transdermal drug system.

(iii) Estimation of heat transport through dermal regions of human body with respect to variable physiological parameters and ambient conditions.

(iv) Mathematical study to identify the effect of porosity, ambient temperature, blood perfusion rate and metabolic heat generation on the thermoregulation of human eye.

1.1 Mathematical modelling

The use of mathematics provides a tool for structuring thoughts for the researchers who create the model and the ones who use it. Mathematical modelling is the description of an experimental delineated phenomenon by means of mathematics, with a view to capturing the silent aspects of the phenomenon at hand. Mathematical modelling is used in different fields like physics, chemistry, biology, pharmacy, biomedical engineering, political science, economics, artificial intelligence, etc.

1.2 Human physiology

The functioning of organs and cellular processes in human body are studied by human physiology in all possible perspectives. It is because of this system, the coordination among various organs is stable and the continuous homeostasis is maintained from macroscopic to molecular level. The working model of body is based on many cells and all of them are responsible for the maintenance of organism. These cells perform various functions as almost all the cells require same procedure for metabolism. To
maintain a constant internal ambience, these cells need certain materials to thrive on, (oxygen, glucose, waste removal, mineral ions and so forth) which becomes necessary for the health of individual cells and ultimately for the whole body. Collectively, the processes involved in the regulation of internal environment is referred to as homeostasis. The concept of homeostasis has been given by French scientist Claude Bernard (1813-1878) and the word homeostasis has been derived from two Greek words—homoios meaning same or resembling and stasis meaning posture or to stand. Under changing conditions of surroundings, the maintenance of stable internal environment needs regular monitoring and adjustments. The adjusting of physiological systems within the body is called homeostatic regulation which is based on three main mechanisms:

(i) the receptor,

(ii) the control centre and

Figure 1.1: Flow chart for mathematical modelling.
(iii) the effector.

The receptor receives information about the changes that occur in the environment. The control centre or integration centre receives and processes information from the receptor. At last, the effector responds to the commands of the control centre by either opposing or enhancing the stimulus. Human body has an ability to stabilise the temperature regulation in a narrow range of environmental temperature. In human body, brain acts as the control centre, the receptor is temperature sensors of body and the effector is blood vessels and sweat glands in the skin. When body feels heat, the temperature sensors in skin send the signals to control centre where from brain sends the message to the sweat glands to increase sweating and increase blood flow to our skin. In the cold conditions, the opposite happens. The brain sends a message to sweat glands to decrease sweating, decrease blood flow and begin shivering. This is an ongoing process that continually works to restore and maintain homeostasis.

Homeostatic systems are ultra-stable. The system is capable of testing the ways in which its variables are adjusted and their whole group (internal, structural and functional) contributes in maintenance of stability. Physiology is largely a study of processes related to homeostasis. Homeostasis is, therefore, a right structure for the introductory study of physiology.

In the present chapter of the thesis, we tried to explain the specific characteristics and mechanisms of the human body responsible for homeostasis and other stable conditions.

1.3 Cardiovascular system

The human cardiovascular system is primarily a transport system in which oxygen, carbon dioxide and nutrients are carried by the blood to and from the various muscles and organs. The cardiovascular system behaves as an internal network connecting all parts of body through a system of blood channels - arteries
and veins; major vessels - arterioles and venules, and small vessels - avenues and capillaries. This system allows continuous delivery of blood to different organs and expulsion of the nutrients, gases, waste products and messages throughout the body [52].

![Figure 1.2: Schematic diagram of cardiovascular system](image)

The cardiovascular system is divided into two circuits as:

(i) **Pulmonary circuit:** The pulmonary circuit consists of heart, lungs, pulmonary veins and pulmonary arteries. The main function of the pulmonary circuit is to pump the de-oxygenated blood from the heart to the lungs through pulmonary artery where it becomes oxygenated and is returned back to heart through the pulmonary vein.

(ii) **Systemic circuit:** The systemic circuit consists of the heart and all the remaining arteries, arterioles, capillaries,
venules and veins. Systemic circulation supplies the oxygenated blood, which has been pumped to the left ventricle of heart by pulmonary circulation, to all the tissues and organs of the body in order to provide them with nutrients and gases responsible for the proper functioning of the organs.

Human body requires energy to perform different functions and this energy is being transported by blood from the digested carbohydrates through digestive tract to different organs. Endocrine glands secrete the hormones which are being transported by the cardiovascular system to their target organs and the waste materials are delivered to the lungs or urinary system to be thrown out of the body.

1.4 **Anatomy of human skin**

Skin is considered as one of the most important organ of the human body. The human skin is known as the largest organ of the human body. It covers the exterior surface of the body and has total surface area of about 20 square feet. Skin covers and protects underlying tissues and organs from microbes, chemicals, ultraviolet radiations and infections. It acts as a barrier between the environment and the underlying tissues and also helps in maintaining the temperature of the human body. Human skin is mainly composed of three different layers - epidermis, dermis and hypodermis (subcutaneous). The schematic diagram of human skin with multi-layered system is given in Figure 1.3 for further information.

**Epidermis**

The epidermis forms the outermost layer of the skin acting as the physical as well as chemical barrier between the interior body organs and external environment. It acts as a protective shield for the body and renews itself after every 28 days. The epidermis
varies in thickness from 0.05mm on the eyelids to 0.8 – 1.5mm on the soles of the feet and palms of the hand. Epidermis is further composed of four different sub-layers:

(i) Stratum basale
(ii) Stratum spinosum
(iii) Stratum granulosum
(iv) Stratum lucidum
(v) Stratum corneum

The stratum basale is the first layer of the epidermis. This is the deepest layer of the epidermis and is at the top of the dermis. It is a single layer of cube-shaped cells. Keratinocytes - new epidermal skin cells are formed in this layer through cell division to replace those shed continuously from the upper layers of the epidermis. This regenerative process is called skin cell renewal. The rate of cell renewal decreases with age. Melanin - photo protective pigment is also present in this layer and protects the skin against ultraviolet radiation [39].

The stratum spinosum forms the second layer of the epidermis. It is sometimes called the prickle-cell layer. The stratum spinosum is composed of 8 – 10 layers of polygonal keratinocytes.
The stratum granulosum or the granular layer forms the third layer of epidermis which is composed of 3 – 5 layers of flattened keratin. Keratin is a tough and fibrous protein which gives skin its protective properties.

The fourth layer in the epidermis is the stratum lucidum or the clear layer. This layer is present only in the fingertips, palms and soles of the feet. It is 3 – 5 layers of extremely flattened cells.

The fifth layer stratum corneum also called horny layer is the outermost layer of the epidermis and is the real protective layer of the skin. Keratinocytes in the stratum corneum are continuously shed by friction and replaced by the cells formed in the deeper sections of the epidermis. In the stratum corneum, there are epidermal lipids (ceramides, fatty acid and lipids) between the keratinocytes which act as cement between the skin cells. The combination of keratinocytes with epidermal lipids forms a waterproof moisture barrier that minimizes transepidermal water loss (TEWL) and keeps moisture in the skin. This moisture barrier protects human body against certain micro organisms and toxic chemicals.

**Dermis**

The dermis region is the main skin layer and is located between the hypodermis and the epidermis. It is a fibrous network of tissue that provides structure and flexibility to the skin. The dermal thickness on an average is about 2mm. The dermis is a mesh-like network composed of collagen and elastin, blood and lymph vessels and specialized cells called mast cells and fibroblasts. This mesh is surrounded by a gel-like substance called the ground substance which is composed of glycosaminoglycans. The ground substance helps in hydration and maintenance of moisture levels within the skin [38].

The blood vessels in the dermis help in thermoregulation of the body by constricting or dilating to conserve or release
heat. They also help in immune function and provide oxygen and nutrients to the lower layers of the epidermis. These blood vessels do not extend into the epidermis. The nutrients diffuse only up to the lowest layers of the epidermis. The oxygen and nutrients do not reach up to the upper layers of the epidermis so the cells present there are dead.

**Hypodermis**

The hypodermis also called the subcutaneous layer is the deepest section of the skin. Its main function is to connect the skin to the underlying bone and muscle, and supplying the nutrients to the skin through blood vessels and nerves.

### 1.5 Anatomy of human eye

The eye is one of the important and most sensitive organs in the human body. The eyes are located in cone shaped cavities in the skull called the orbits or socket which protects them against any injury. The eye is a spherical organ which measures approximately one inch or 2.5 cm in diameter. It is composed of the following three main layers:

(i) Fibrous layer

(ii) Vascular layer

(iii) Retina

Apart from these layers, there are other parts like lens, aqueous humour and vitreous humour as shown in Figure (1.4). Each of these layers have different functions to perform. The fibrous layer of eye tissue allows light to enter into the eye, nourishes the eye and controls the amount of light to enter into the eye. The vascular layer helps in protecting the different portions of eye. The retina is the sensitive portion of eye which converts the image into electrical impulse to be interpreted by brain. The detailed description of different layers of eye is given below:
Fibrous layer

Fibrous layer is the thick and tough layer which protects the eyeball. It also helps in maintaining the shape and form of eyeball. This layer has two distinct and unequal regions via

(a) sclera
(b) cornea

(a) Sclera: It forms the posterior five-sixth of the fibrous layer. It is commonly known as “the outer wall of the eye”. It is tough, opaque and bluish-white. It is largely hidden in the orbit. The sclera serves to support and protects the inner parts of the eye. It contains about 68% of water.

(b) Cornea: It forms the anterior one-sixth of the fibrous layer. The cornea is the transparent, dome-shaped window covering the front of the eye. This contains 78% of water. An adult cornea has a front surface of radius about 8mm. The cornea helps in the image formation by refracting light entering into the eye. The cornea is a non-vascular structure as the capillaries that supply nutrients to the cornea terminate in loops at its circumference.

Vascular layer

The vascular layer is the middle layer of the eye tissue which contains much of the eye’s pigment. The vascular layer or Uvea consists of three regions

(a) Choroid
(b) Iris
(c) Ciliary body

(a) Choroid: The choroid is also known as the choroid-ea or choroid coat and it lies in the region between the retina and
sclera. This section of vascular layer is dark brown in colour containing blood vessels and gives nourishment to our eyes.

(b) Iris: The iris is that part of the vascular layer of the eye tissue which determines a person’s eye colour (blue, green, brown). This is a pigmented tissue which lies behind the cornea and in front of the natural lens. The iris acts as a camera shutter which controls the amount of light entering the eye. There is a small opening in the center of iris called pupil. The pupil is small in bright light and large in dim light. The size of pupil usually varies with age.

(c) Ciliary body: The ciliary body is located behind the iris and acts as an instrument for controlling the focusing of the eye and the production of aqueous fluid. The ciliary body is a well-vascularized tissue with high rate of blood flow.

Retina

The retina is a multi-layered sensory tissue that lies at the back of eye and contains millions of photo-receptors that capture light rays and convert them into the electrical impulses which travel to brain through optic nerve where they are turned into images. Retina is separated into two layers - the outer layer or pigmented layer which absorbs light as well as removes damaged and dead photoreceptor cells. This layer also helps to recycle the vitamin A product that is very essential for eye’s nourishment. The second layer is the inner layer or the neural layer which contains the photo-receptors and other cells that allow a person to see.

There are mainly two types of shapes for the photo-receptors in the retina namely rods and cones. There are nearly about 6 million cones which are contained in macula - that portion of retina which is responsible for vision. Cones are used for day vision and in order to function these needs a lot of light. The rod type of photo-receptors are about 125 million in number, they
are responsible for night vision and lack of them causes night blindness.

![Figure 1.4: Schematic diagram of multi-layered human eye](64)

**Lens**

Lens is located directly behind the iris which helps to focus the rays of light onto the retina. The softer material called cortex surrounds the innermost part of the lens (nucleus). The lens is encased in a capsule like bag and suspended within the eye by tiny wires called Zonules. There is about 65% of water in lens and it decreases with ageing. The lens is separated from aqueous chamber by capsule posterior and the epithelium capsule anterior, so any damage to the capsule may lead to the occurrence of the cataracts.

**Aqueous humour**

The watery fluid that is continually secreted by the ciliary body fill the space between the cornea and iris. This fluid nourishes the cornea and the lens, and also gives the front of eye its shape and form.
Vitreous humour

The chamber lying behind lens and in front of the retina is filled with a gelatinous fluid called the vitreous humour. It is composed of water and comprises about $\frac{2}{3}$ of the eye’s volume. The main function of vitreous humour is to retain the eye to its actual shape when compressed.

1.6 Diffusion in biological tissues

Diffusion in any medium is defined as the movement of molecules from the region of high chemical potential to the region with low chemical potential. In other words, it may be defined as the movement of any substance from an area with higher concentration to an area of lower concentration. The word diffusion has been derived from the Latin word “diffundere” meaning “to spread out”. In general, diffusion can be defined as the impulsive spreading of particles, heat or momentum. Diffusion does not need any energy expenditure as it is a physical process. Diffusion occurs due to the second law of thermodynamics, according to which the entropy of any closed system should always increase with time.

Any substance will move into the space available for it until it gets evenly distributed throughout it. There will be no net movement from one region onto another after a substance has diffused completely. This is known as dynamic equilibrium. There are several factors that affect the rate of diffusion. Few of them are as follows:

(i) **Particle size:** The rate of diffusion is inversely proportional to the size of a molecule. At a given temperature, a heavier and larger particle will move slowly as compared to the lighter and smaller one.

(ii) **Temperature:** The rate of molecular movement increases with increase in temperature and hence increases the rate
of diffusion.

(iii) **Concentration gradient:** The rate of diffusion is directly related with the concentration gradient. Diffusion will occur only when concentration gradient exists otherwise there will be no net diffusion when the gradient is zero.

(iv) **Distance:** For a given particle to diffuse a farther distance, it will take longer time and hence, the rate of diffusion is slow.

(v) **Surface area:** The rate of diffusion is directly proportional to the surface area. This implies that greater the surface area of the membrane, the greater will be the probability for a particle to pass.

There are two ways to have the better understanding of diffusion - either the phenomenological approach starting with Fick’s laws of diffusion and their mathematical consequences; or a physical and atomistic one, by considering the random walk of the diffusing particles. In the phenomenological approach, diffusion is simply the movement of a substance from a region of high concentration to a region of low concentration without bulk motion and from the atomistic point of view proposed by Robert Brown, diffusion is considered as a result of the random walk of the diffusing particles.

The two basic laws that are used in the diffusion models have been proposed by Adolf Fick, the 26-year old anatomy demonstrator from Zürich in 1855. The Fick’s law is analogous to the Fourier’s law for heat conduction, Ohm’s law for electric current and Darcy’s law for hydraulic flow.

**Fick’s first law of diffusion**

According to Fick’s first law, the flux is directly proportional to the concentration gradient, i.e., the direction of flux goes from regions of higher concentration into the regions of lower
concentration. In one dimensional form, we have

\[ J = -D \frac{\partial C}{\partial x} \]

where \( J \) is the amount of substance that will flow through a small area in a small time interval, \( D \) is the diffusion coefficient, \( C \) is the concentration and \( x \) is the position vector. Here, negative sign indicates the direction of decrease of concentration.

To derive Fick’s first law in one dimension, consider a group of particles performing a random walk of length \( \Delta x \) in time \( \Delta t \). Let the number of particles at position \( x \) at time \( t \) be \( N(x, t) \). At any time step, half of the particles would move towards left and half towards right. At point \( x \), half of the particles move to right and at \( x + \Delta x \), half of the particles shift to left, so the net movement of particles to the right is

\[ -\frac{1}{2} \{ N(x + \Delta x, t) - N(x, t) \}. \]

Since the flux \( J \) is defined as this net movement of particles across some element having an area \( a \) normal to the random walk during a time interval \( \Delta t \). Hence, we have

\[
J = -\frac{1}{2} \left\{ \frac{N(x + \Delta x, t)}{a \Delta t} - \frac{N(x, t)}{a \Delta t} \right\}
\]

\[ = -\frac{(\Delta x)^2}{2a \Delta t} \left\{ \frac{N(x + \Delta x, t)}{a(\Delta x)^2} - \frac{N(x, t)}{a(\Delta x)^2} \right\}. \quad (1.6.1) \]

Since concentration is defined as particles per unit volume. Hence,

\[ C(x, t) = \frac{N(x, t)}{a \Delta x}, \]

also, \( \frac{(\Delta x)^2}{2a \Delta t} \) is defined as the diffusion constant \( D \) in one dimension.

So, equation (1.6.1) reduces to

\[
J = -D \left\{ \frac{C(x + \Delta x, t)}{\Delta x} - \frac{C(x, t)}{\Delta x} \right\}. \quad (1.6.2)
\]
Taking limit $\Delta x \to 0$ in equation (1.6.2), we have

$$ J = -D \frac{\partial C}{\partial x}. \quad (1.6.3) $$

**Fick’s second law of diffusion**

Fick’s second law describes that the rate of accumulation or depletion of concentration within the volume which is proportional to the local curvature of the concentration gradient.

i.e.,

$$ \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2}. $$

Fick’s first law and the mass of conservation are used in the derivation of Fick’s second law. According to law of conservation of mass, we have

$$ \frac{\partial C}{\partial t} + \frac{\partial J}{\partial x} = 0 $$

$$ \frac{\partial C}{\partial t} + \frac{\partial}{\partial x} \left( -D \frac{\partial C}{\partial x} \right) = 0. $$

Assuming $D$ to be constant, we have

$$ \frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} $$

which is similar to the heat equation.

**1.7 Thermoregulation in human body**

Based on the blood temperature of living creatures, the living animal species were classified into two major categories - cold blooded and warm blooded animals. Those animals whose body temperature show the fluctuation with the changing ambient temperature are called as cold blooded animals while as warm blooded animals are those who maintain their body core temperature with the changing environmental conditions such as human beings. The normal functioning of the body and its
survival depends on the ability of the human body to control and maintain body temperature within the range necessary for its existence. It is well known that the temperature of each human organ and entire body should remain within the range of $0 - 42^0C$, with most of the internal temperatures controlled within the range of $35 - 39^0C$. Any interruption to this range may lead to the malfunctioning of the human organs. For example, if the temperature of the brain gets exceeded then it may suffer to an irreversible damage, and the functioning of the other organs such as heart may get slowed down or even impaired if the temperature gets too low within this range. Human beings have the body temperature relatively constant, despite significant changes in the external environmental conditions. In order to maintain a constant core temperature, the human body balances the amount of heat it produces and absorbs with the amount it loses. This process is known to be thermoregulation and the cardiovascular system plays an integral part. Thermoregulation maintains the core temperature at a constant set point, averages $36.2^0C$, despite fluctuations in heat absorption, production and loss.

The thermoregulatory response of human body is mainly determined by reaction from the thermoreceptors. The control centre for body temperature and central thermosensors are located in the hypothalamus. The peripheral thermoreceptors located in the skin and central thermoreceptors located in the body core sends the afferent input to the hypothalamus. Both sets of information are essential for the body to make appropriate adjustments. The hypothalamus sends impulses to different effectors within the body to adjust the temperature. Two main centres in the hypothalamus are responsible for the temperature control- the posterior one responsible for the protection against cold and the anterior one, for the protection against heat.

When any fluctuation in temperature is recorded the hypothalamus reacts by initiating certain mechanisms in order to
retain the normal temperature. These adjustments in temperature can occur at four different sites which are summarized as:

(i) **Sweat glands:** When the blood or skin temperature is measured to be above the normal temperature, the sweat glands present on the skin surface are instructed to develop sweat onto the surface of the skin. This helps the excessive heat to be lost through evaporation and makes the skin cool by convection which in turn causes the cooling effect on the blood.

(ii) **Endocrine glands:** When the blood temperature is below the normal temperature, the hypothalamus activates the secretion of hormones such as thyroxin, adrenalin and noradrenalin. All the hormones increase the metabolic heat generation and thereby, increases the blood temperature.

(iii) **Skeletal muscle:** When the temperature of the peripheral tissues reduces below the normal temperature, the hypothalamus reacts by causing skeletal muscles to start shivering. Shivering is very fast but small muscular contractions.

(iv) **Smooth muscle around arterioles:** When there is increase in temperature, the smooth muscle in the walls of arterioles are relaxed resulting in vasodilation i.e. increase in the diameter of the blood vessels. Vasodilation in turn increases the flow of blood to the skin and causes cooling. On the other hand, when the thermoreceptors feel cooling of the blood or skin, then the hypothalamus sends a message to the smooth muscle of the arteriole walls causing the arterioles to reduce their diameter which is called vasoconstriction. This leads to the reduction of blood flow to the skin and therefore helps to maintain body temperature.

Every living organism produces heat and this heat is either lost to the environment or is stored in the body. There are two
main mechanisms involved with the heat production and heat loss which are discussed briefly as:

**Thermogenesis**

Human body can perform various function using stored energy. The main source for the energy is food. Animals need food to support all life processes including breathing, circulation, movement, nerve functions and temperature regulation. Animals use several physiological and behavioural mechanisms to maintain their body temperature and minimize the loss of energy. Metabolism is the main process responsible for the generation of heat in body and the process of generation of heat is called thermogenesis. All the changes that occur in digested food stuffs in our body through absorption and elimination is termed as metabolism.

Metabolic regulation of body heat is an important aspect of the human physiological thermoregulatory response. In cold conditions, the metabolism will speed up, causing an increase in thermogenesis and conversely, in warmer environments the metabolism will slow down, causing a decrease in thermogenesis. The level and efficiency of the metabolism is regulated by several hormonal and neuro-regulatory mechanisms. The overall heat gain in the body is termed as thermogenesis.

**Thermolysis**

In case there is increase in body core temperature, the autonomous system of the body tries to transfer the excessive amount of heat to the environment and similarly, when there is heat loss, body regulates and generates heat from the stored energy and surroundings. The processes involved in this heat transfer are conduction, convection, radiation, evaporation, etc.
Conduction

Conduction is the transfer of the heat across a medium from a source of higher temperature to a source of lower temperature due to the physical contact. The conduction process of heat energy will occur until the thermal equilibrium is attained. Heat conduction is governed by the Fourier Law of diffusion which states that the heat flux $q$ is proportional to the temperature differences per unit length.

$$q = -\lambda \frac{\partial T}{\partial x}$$

where the proportionality constant $\lambda$ is the thermal conductivity of the material.

Convection

Convection is the exchange of body heat with the external environment. If the body temperature is higher than its external ambient temperature, then heat flows from the body to the surrounding air causing it to heat up is replaced by the more dense and cool air at the peripheral regions of the body. Thus, cool air which moves continuously up to the body surface gets warmed by body heat and then flows away. This results heat loss from the body surface. Therefore, the transfer of heat to a moving fluid is termed as convection.

The heat loss due to the forced convection is given by the Newton’s law of cooling (1.7.1)

$$q_c = h \mathcal{A} (T - T_a)$$

(1.7.1)

where

$q_c = \text{rate at which heat is transferred}$,
$T = \text{body surface temperature}$,
$T_a = \text{ambient temperature}$,
$h = \text{convective heat transfer coefficient}$,
$\mathcal{A} = \text{exposed surface area}$.
Radiation

Radiation is another means of heat exchange between human body and surroundings through infra-red rays. All objects including human body that are not at the absolute temperature radiate heat energy from such rays. Human body radiate heat rays in all directions. However, walls and the other objects radiate heat rays towards the body surface.

Evaporation

Energy is required when fluid passes from a liquid to the gaseous state. Evaporation of sweat from the skin is also quantified as heat loss from the body. When one gram of water evaporates from body surface, 0.58 kilocalories of heat is lost from the body. Evaporation removes heat from the skin and cools it in the process. Water evaporates insensibly from the skin and lungs at a rate of about 600ml per day. This causes continual heat loss at a rate of 12 to 16 calories per hour. The rate of evaporation is increased during hot conditions and in exercise. The amount of heat loss during vaporization depends upon the surface area, temperature gradient, humidity, vapour pressure gradient and the rate of airflow over the surface.

1.8 Pennes’ bio-heat equation

Heat transfer in living tissues is a complex process as it includes conduction, convection, radiation, metabolism, evaporation and inherent temperature regulation. Blood perfusion has a remarkable effect on the temperature distribution in the living tissues. In 1948, Pennes was the first to propose and validate experimentally an analytical bio-heat transfer model with a heat loss term due to blood perfusion \[46]. He suggested that the rate of heat transfer between blood and tissue is proportional to the product of the volumetric perfusion rate and the difference between the arterial blood temperature and the local tissue tempera-
ture. The following mathematical relationship in this direction is given below [59]

\[ h_p = \omega \rho_b c_b (1 - \nu) (T_A - T) \]  

(1.8.1)

where \( h_p \) is the rate of heat transfer per unit volume of tissue, \( \omega \) is the perfusion rate per unit volume of tissue, \( \rho_b \) is the density of blood, \( c_b \) is the specific heat of blood, \( \nu \) (0 ≤ \( \nu \) ≤ 1) is a factor that accounts for incomplete thermal equilibrium between blood and tissue, \( T_A \) is the arterial blood temperature, and \( T \) is tissue temperature. He assumed \( \nu = 0 \) when he computed his theoretical curves and also incorporated the effects of metabolism.

The bio-heat equation is extensively used in the investigation of many heat transfer problems with biomedical applications. The general bio-heat equation is

\[ \rho c \frac{\partial T}{\partial t} = \nabla (\lambda \nabla T) + \omega \rho_b c_b (T_A - T) + S \]  

(1.8.2)

where  
\( c = \) tissue specific heat;  
\( \rho = \) tissue density;  
\( \lambda = \) tissue thermal conductivity;  
\( S = \) rate of metabolic heat generation;  
\( t = \) time.

The first term on the right side of the equation accounts for the heat being conducted through the various layers of tissues with differing thermal properties using Fourier’s Law. The second term of the bio-heat equation accounts for the heat transfer due to the blood flow (also referred to as perfusion) within the body’s circulatory system. Finally, the third term is used to represent the heat that is generated due to natural metabolic processes in the body and external heat generation sources. The metabolic heat generation refers to the heat produced in the body as a result metabolic activities.
One of the main advantage of the Pennes’ model is that the blood perfusion term which accounts for the heat transfer in living tissues is linear in temperature facilitates the solution of equation (1.8.2). Many investigations were carried out on the thermal disturbances in human tissues. To describe the heat transfer process in human body, it is very difficult to construct generally applicable models and most of the proposed models are very sophisticated. The complexity about the geometry of human body makes most of the thermal models difficult to solve analytically and hence many of the equations have been solved by different numerical methods like finite difference method, finite element method, boundary element method, etc. Kai et al. [60] derived the analytical solution for one dimensional steady state Pennes’ bio-heat equation in cylindrical coordinates and analysed the effects of thermal conductivity, blood perfusion, metabolic heat generation and heat transfer coefficient on tissue temperature. Rodrigues et al. [48] obtained an analytical solution by Bessel series for one dimensional transient bio-heat equation in a multi-layer human regions with spatially dependent heat sources. Cheng and Liu [7] used the Pennes’ bio-heat equation in spherical coordinates to describe the heat transport occurring in biological tissues during magnetic tumor hyperthermia. Tzu-Ching Shih et al. [53] used Laplace transform technique to find out the effect of the temperature response of a semi-infinite biological tissue due to a sinusoidal heat flux at the skin. Wang and Qin [57] used finite element method to study the steady-state temperature distribution inside multi-layer human skin and subcutaneous tissues with burn injuries. Saxena and Khanday [24-30] had carried out a notable research for the study of heat distribution in biological tissues. Khanday [26] studied the temperature distribution in multi-layered human skin and sub-cutaneous (SST) by assuming the thermal conductivity as a function of temperature. Khanday et al. [27,28] studied the diffusion of heat and mass in biological
tissues particularly dermal regions and human head. They [29], [30] also studied heat distribution patterns in multi-layered human eye using one dimensional transient heat equation using FEM and Laplace transform techniques. Vyas and Rustgi [56] used Green’s function method to study the temperature regulation by laser interaction with tissue. Deng and Liu [13] used Green’s function method to analyse the temperature behaviour of living tissues subject to constant, sinusoidal, step, point or stochastic heatings at the skin surface.

1.9 Pharmacokinetics

In 1953, a German paediatrician F. H. Dost was first person to introduce the term pharmacokinetics. Pharmacokinetics is a combination of two Greek words - pharmakon meaning drugs and poisons, and kinetikos meaning moving or putting in motion. Pharmacokinetics does not deal with the effect of drug on the disease but deals with the behavior of an administrated drug in the body over time. It attempts to discover the process of a drug from the moment of its administration up to its elimination from the body.

ADME is the process that describes the disposition of the pharmacological substances within human body i.e. absorption, distribution, metabolism and excretion. Drug absorption is the movement of a drug into the bloodstream after administration. Absorption is the study about the flow of drug from its ingestion starting from the stomach up to the bloodstream. Distribution demonstrates the movement of drug from bloodstream to the different organs of the body. Metabolism studies the degradation of drug within the body and excretion is all about the elimination of drug from the body.

The digestive system of the body is involved in the intake, breakdown, transport, absorption and metabolism of food and the removal of waste products. The system includes the oral cavity, gastrointestinal (GI) tract, liver, gallbladder and pancreas.
The gastrointestinal tract consists of the oesophagus, stomach, small and large intestines and rectum. The function of the gastrointestinal tract is to break down food, transport the nutrients across intestinal epithelium, store and remove waste products, etc. These functions require the coordinated action of the gastrointestinal tract with all the organs of the digestive system.

The liver performs essential metabolic activities including heptic flow of the body, removing toxic molecules from the blood, and serving an important immune function. Because the liver processes molecules from food and the body, it has a dual blood supply. The portal vein transports 80% of the blood to the liver and carries blood from the intestines. The remaining 20% of blood flow comes from the heptic artery, a branch of the celiac artery.

The kidneys are responsible for the removal of waste products such as urea, for fluid and ion balances, and for the regulation of the blood pressure. Filtration of the blood plasma and re-absorption of water and ions remove waste products and maintains balance in the system. The kidneys account for about 0.5% of the body weight, but receive 23% of the cardiac output (1.25 L min$^{-1}$). Such large flow rates are needed in order to filter blood efficiently.

**Routes of administration**

Many drugs can be administered orally in the form of liquids, capsules, tablets or chewable tablets. The oral route is often used for drug administration due to the fact that it is most convenient and usually the safest and least expensive medication. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its
target site. The intestinal wall and liver chemically metabolize many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect.

When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, some with food, some should not be taken with certain other drugs, and still others cannot be taken orally at all. Some orally administered drugs irritate the digestive tract. For example, aspirin and most other nonsteroidal anti-inflammatory drugs can harm the lining of the stomach and small intestine to potentially cause or aggravate preexisting ulcers. Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Intravenous administration is the another way to deliver a precise drug dosage quickly and in a well-controlled manner throughout the body. Intravenous simply means “within veins” and in this, a needle is inserted directly into a vein. The drug is given in the solution form either as a single dose or by continuous infusion. For infusion, the solution is moved by gravity (from a collapsible plastic bag) or by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. When a drug is delivered intravenously, it gets immediately mixed to the bloodstream and effects more quickly than any other route. In some critical conditions or emergency, effect of a single drug dosage lasts for a shorter time. In such cases, drugs must be given by continuous infusion in order to keep their effect constant.

Some drugs are delivered body-wide through the transdermal patch on the skin. Transdermal drug delivery (TDD) is a feasible administration route for potent, low-molecular weight therapeutic agents which cannot resist the aggressive environment of the GI tract or those drugs that gets quickly eliminated
from the human body. The selection of therapeutic agent is determined by several factors including the physiocochemical properties of the drug, its biological properties and its interactions with the membrane and pharmacokinetic and pharmacodynamic properties of the drug. The release of a therapeutic agent from its formulation is applied to the skin surface and its transport to the systemic circulation is a multi-step process as shown in Figure 1.5 describes the following:

(a) dissolution within and release from the formulation,
(b) partitioning into the skin’s outermost layer, the stratum corneum,
(c) diffusion through the stratum corneum, principally via lipidic inter-cellular pathway,
(d) partitioning from the stratum corneum into the aqueous viable epidermis,
(e) diffusion through the viable epidermis and into the upper dermis, and

(f) uptake into the local capillary network and eventually the systemic circulation.

The drugs used through dermal system are sometimes mixed with a chemical like alcohol that enhances penetration through the skin into the bloodstream without any injection. In order to have the constant levels of drug in the bloodstream, the drug can be delivered slowly and continuously for many hours or days or even longer times through this patch. Some drugs given through the patches include nitroglycerin used to relieve chest pain, scopolamine used for motion sickness, nicotine to cure smoking cessation, clonidine to control high blood pressure and fentanyl as a pain relieving drug.

Transdermal route of administration cannot be employed for all types of drugs. The most important requirement of drug to be delivered transdermally is demonstrated by need for controlled delivery, such as short half-life, adverse effect associated with other route or a complex oral or intravenous dose regimen [4].

1.10 Reaction kinetics

Reaction kinetics are described in terms of reaction rate $k$, which represents the amount of reactant consumed or product produced per unit time. The rate of a chemical reaction is influenced by various factors. Some of them are:

(i) **Nature of reaction**: The rate of a reaction is greatly influenced by the physical state of the reactants, the number of molecules and the complexity of the reaction.

(ii) **Concentration**: Reaction rates are greatly affected by the concentration of the reacting substances as increase in con-
centration leads to the increase in the collision of reacting molecules resulting in the increase in reaction rates.

(iii) **Pressure:** Increase in pressure increases the rate of gaseous reactions. The reaction rate increases in the direction where there are fewer moles of gas and decreases in the reverse direction.

(iv) **Temperature:** The reaction rate is increased with the increase in temperature by causing more collisions between the particles.

The rate of a combination of the drug $\mathcal{D}$ and receptor $\mathcal{R}$ is proportional to the concentrations of the drug and receptor

$$[\mathcal{D}] + [\mathcal{R}] \xrightleftharpoons[k_2]{k_1} [\mathcal{C}]$$

where

- $\mathcal{C}$ = drug-receptor complex,
- $k_1$ = association rate constant,
- $k_2$ = dissociation rate constant.

Hence, $k_d = \frac{k_2}{k_1} = \frac{[\mathcal{D}][\mathcal{R}]}{[\mathcal{C}]}$ where $k_d$ = dissociation constant

and association constant $k_a = \frac{1}{k_d} = \frac{k_1}{k_2} = \frac{[\mathcal{C}]}{[\mathcal{D}][\mathcal{R}]}$.

### 1.11 Mathematical techniques

Different mathematical techniques and methods can be used to solve the formulated models involving mathematical terms. But, for the most part of our study, we make use of Laplace transform, finite element method, finite difference method, eigenvalue expansion, etc for the solution purpose. Also, for the computational analysis MATLAB software has been used.
Finite element method (FEM)

The finite element method or finite element analysis (FEA) is one of the most popular and advanced mathematical cum numerical technique used for finding out the approximate solutions to various complex boundary value problems arising in different engineering and scientific fields. Richard Courant, German mathematician probably be credited for developing finite element method [11]. The development of this method became effective with the advent of computers and is now recognized as one of the most powerful and versatile method for construction approximations of the solutions of boundary-value problems. Finite element method when compared to the other numerical methods is very powerful in its application to the real world problems which involve complicated geometries and boundary conditions. Initially, FEM was used for solving problems in aeronautical and civil engineering. Later on, this method was generalized for a broader range of differential equations, with applications in fluid mechanics and structural dynamics.

In the finite element method, the domain of the problem is partitioned into smaller and simpler number of sub-regions called finite elements and each element is represented by a set of element equations followed by assembling all sets of element equations to get a global system of equations for the final calculation. In finite element method, the solution is approximated by any variational methods from the calculus of variations in order to minimize an associated error. The division of whole region into smaller elements in finite element method is very fruitful. This division helps to get the precise representation of complex geometries, incorporates the dissimilar material properties and gives simpler representation of the total solution.

**Definition 1.** A functional is defined as any function whose domain is a set of admissible functions.

Mathematically, \( I : S \rightarrow \mathbb{R} \) where \( S \) is the set of admissible functions, is a functional.
Theorem 1. [Euler Lagrange’s Differential Equation]

A functional \( I(y(x)) = \int_a^b f(x, y, y') dx \) satisfying the boundary conditions \( y(a) = \alpha \) and \( y(b) = \beta \) will attain its optimum value on the curve \( y = y_0(x) \), if

\[
\frac{\partial f}{\partial y} - \frac{d}{dx} \left( \frac{\partial f}{\partial y'} \right) = 0
\]

(1.11.1)
on \( y = y_0(x) \).

Laplace transform

The Laplace transformation is one of the mathematical tools that is helpful in finding out the solution of various problems in science and engineering. In 1970 Laplace, a French mathematician used this transform in his work on probability theorem. This method became popular when Heaviside applied it for finding the solution of an ordinary differential equation related to a problem in electrical engineering. Later, Carslaw and Jaeger [6], Churchill [10], Jaeger [20], Tranter [55] and others contributed a lot in the field of Laplace transform and its applications.

Laplace transform method is very advantageous in finding the solution of an ordinary differential equation with appropriate initial conditions, without first finding the general solution and then using initial conditions for evaluating the arbitrary constants, as this method reduces the solution of an ordinary differential equation to the solution of an algebraic equation. Application of Laplace transform technique to partial differential equation reduces the number of independent variables by one.

Definition 2. A function \( f(t) \) is said to be of exponential order \( \gamma_0 \), if \( f(t) \) is a piecewise continuous function and there exists a real number \( \gamma_0 \) and a finite positive \( M \) such that

\[
Lt_{t \to \infty} |f(t)|e^{-\gamma t} \leq M \quad \text{for} \quad \gamma > \gamma_0
\]

(1.11.2)
and the limit does not exist when $\gamma < \gamma_0$.

**Definition 3.** Let $f(t)$ be a continuous and single-valued function of the real variable $t$ defined for all $t, \ 0 < t < \infty$, and is of exponential order. Then the Laplace transform of $f(t)$ is defined as function $F(s)$ given as

$$\mathcal{L}\{f(t); s\} = F(s) = \int_0^\infty e^{-st}f(t)\,dt \quad (1.11.3)$$

over that range of values of $s$ for which the integral exists. Here, $s$ is a parameter, real or complex. Thus,

$$\mathcal{L}\{f(t); s\} = F(s)$$

and $f(t) = \mathcal{L}^{-1}\{f(s); t\}$

where $\mathcal{L}$ is the operator which transforms $f(t)$ into $F(s)$, called Laplace transform operator, and $\mathcal{L}^{-1}$ is the inverse Laplace transform operator.

**Note:** Laplace transform is usually denoted by the symbol $\hat{f}$ or $\mathcal{L}\{f(t)\}$.

**Theorem 2.** If $f, f', \ldots, f^{(n-1)}$ are continuous on $[0, \infty)$ and are of exponential order and $f^{(n)}$ is piecewise continuous on $[0, \infty)$, then

$$\mathcal{L}\{f^n(t)\} = s^nF(s) - s^{n-1}f(0) - s^{n-2}f'(0) - \ldots - f^{(n-1)}(0) \quad (1.11.4)$$

where $F(s) = \mathcal{L}\{f(t); s\}$.

**Theorem 3.** [Heaviside Expansion Theorem]

Let $F(s)$ and $G(s)$ be two polynomials in $s$ where the degree of $F(s)$ is lower than that of $G(s)$ and if $G(s)$ has $n$ distinct
roots $\alpha_i (i = 1, 2, \ldots, n)$, then
\[
\mathcal{L}^{-1} \left[ \frac{F(s)}{G(s)}; t \right] = \sum_{i=1}^{n} \frac{F(\alpha_i)}{G'(\alpha_i)} e^{\alpha_i t}
\]
where $'$ represents the derivative.

**MATLAB software**

MATLAB - MATrix LABoratory, developed by Cleve Moler in the late 1970's at the University of New Mexico and other locations with support from the National Science Foundation. MATLAB is a high-performance language used as a scientific and numerical computing tool. It is the fourth generation programming language. It integrates computation, visualization, and programming in a user friendly atmosphere where problems and solutions are articulated in common mathematical notation. It is used for mathematical computation, algorithm development, modelling, simulation, data analysis, investigation and visualization, plotting of functions and data, scientific and engineering graphics, etc. MATLAB works through three main windows which are:

(i) command window,

(ii) figure window and

(iii) editor window.

When a user opens the MATLAB software command window appears on the screen. It is characterised by the MATLAB command prompt (>>). All commands are typed in this window at the MATLAB prompt. The output of all the graphic commands can be seen on a separate window called the figure or graphics window. The user can create so many figure windows depending upon the system memory. Editor window is that window where the user can write, edit, create and save his own programs as special files called M-files.

Some commands used in MATLAB software are:
<table>
<thead>
<tr>
<th>Command</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>linspace</td>
<td>used to create a linearly spaced vector</td>
</tr>
<tr>
<td>det</td>
<td>used to find the determinant of a matrix</td>
</tr>
<tr>
<td>eig</td>
<td>used to compute the eigen values of a matrix</td>
</tr>
<tr>
<td>inv</td>
<td>to find the inverse of a matrix</td>
</tr>
<tr>
<td>rank</td>
<td>to find the rank of a matrix</td>
</tr>
<tr>
<td>roots</td>
<td>to find the roots of a polynomial</td>
</tr>
<tr>
<td>plot</td>
<td>used to draw the figure</td>
</tr>
<tr>
<td>gtext</td>
<td>add a piece of text to the current plot</td>
</tr>
<tr>
<td>title</td>
<td>add title to the current plot</td>
</tr>
</tbody>
</table>

The above information gives us the basic information about the MATLAB software. There is an extensive applications of this software in almost all disciplines of life sciences, physical science, chemical sciences, social sciences, etc.